REMARKS

Claims 1, 3-11, 15, 16, 18-26 and 69 remain before the Examiner for reconsideration. Claims 12-14, 17 and 27-68 have been withdrawn. Claims 2, 70-103 have previously been canceled without prejudice. New claims 113-116 have been added.

In the Office Action dated April 1, 2010 the Examiner rejected Claims 1,3-11,15-16,18-20,22,25,69,104-11 and 112 under 35 U.S.C. 102(e) "as being anticipated by Beckman et al. (US 7,264,823 B2), for the reasons set forth in the office action filed 11/30/2007."

The Examiner rejected Claims 1,3-4,7-8,12,19,22,27-30,33,69,104-105,108 and 109 under 35 U.S.C. 102(e) "as being anticipated by Woodhouse et al. (US 6,221,997 B1), for the reasons set forth in the office action filed 11/30/2007."

The Examiner rejected Claims 1,3-11,15-16,18-26,69 and 104-112 under 35 U.S.C. 103(a) "as being unpatentable over Zhang et al. (Biomaterials 21 (2000) 1247-1258) in view of Liptova et al. (Macromol. Symp. 152, 139-150 (2000)) or in view of Woodhouse et al. (US 6,221,997 B1), for the reasons set forth in the office action filed 11/30/2007."

With regard to Applicant's arguments filed December 21, 2009, the Examiner asserted that:

> Applicant's arguments filed 12/21/2009 have been fully considered but they are not persuasive.
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> Applicants assert that none of the references above describe the reaction between a multifunctional isocyanate with a bioactive agent in water. Applicants assert that water exerts an effect on the reaction in that it acts as a chain extender; therefore the examiner cannot ignore the limitation as this leads to a patentable distinction in the chemical composition and physiochemical properties of the polymer.
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> The examiner respectfully disagrees. Applicant's arguments revolve around their belief that the chain extender water leads to a patentable difference over the prior art cited above in regards to the chemical composition and physiochemical properties of the polymer. However as currently amended there is no physical or chemical differences claimed to preclude the prior art cited above. The examiner notes that applicant's claims are drawn to a polymer composition formed from the reaction of an isocyanate, water as a chain extender and a bioactive agent. Whatever role water plays in the reaction sequence it does not change the chemical structure, the fundamental repeat unit (-RNHCOOR-)n or (-RNHCONHR-)n of the polymer formed by the reactants claimed. Applicants have not met their burden to explain how their claimed polymers structure would be different than that of the prior art. While the limitation detailing the use of aliphatic isocyanates and a bioactive agent containing at least one reactive group must be considered by the examiner since their use changes the structure of the polymer, the chain

extender, water does not change the chemical structure or physiochemical property of the polymer. Chain extenders are generally used in the art to functionalize the end groups of a macromolecule or prepolymer, allowing it to further react with another polymeric block, increasing the overall molecular weight of the polymer. Chain extenders are generally used to increase the molecular weight of a polymer; however applicants do not claim a molecular weight within their own claims that would preclude any of the references above. Thus the only physical characteristic of the polymer that would be affected by the chain extender water is not present within the claims. Furthermore applicants note at paragraph [0008] within their own specification that Zhang and coworkers used water as chain extenders for the prepolymers, Zhang also states that water is used as a chain extender within the abstract.

In regards to Beckman applicants assert that if Beckman used water in the reactions to form the adhesives it would not be capable of forming adhesive bonds since water would react with the isocyanate functionality, therefore there would be no diisocyante end groups available for attachment.

Once again applicants are attempting to limit their composition by the process to make it not the product itself and not the product itself. If applicants believe there is a difference between their claimed polymer end group and Beckman then they should limit the end group of the polymer in the claims. As noted above the chain extender water does not change the fundamental polymeric formula of the polyurethane or polyurea, water only server to increase the molecular weight of the polymer itself, since applicants do not limit the molecular weight of their polymer the product by process limitation of using water as a chain extender bears no weight on the patentability of the product. As currently amended there is no limitation on the type of end group present on the polymer itself that would preclude Beckman.

Applicants assert that their claimed polymer composition is formed from the simultaneous reaction of the multi-functional isocyanate with bioactive agent and water.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., simultaneous reaction of multi-functional isocyanate with bioactive agent and water) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. *See In re Van Geuns*, 988 F.2d 1181,26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants argue in regards to Woodhouse that this reference does not teach reaction of an amine or an oligopeptide directly with a multi-functional isocyanate as presently claimed.

The relevance of this assertion is unclear; Woodhouse clearly teaches reacting a diisocyanate with a polyol (claimed as additional ingredient in claim 4) and a chain extender that includes an amino acid oligopeptides, meeting the claimed bioactive agent.

Applicants further assert there is no disclosure or suggestion within Zhang that details the reaction of a protein or any other bioactive agent with a multifunctional isocyanate compound and Zhang does not even mention what is meant by incorporation of proteins and therefore is not enabled for attachment of proteins.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re

> Merck & Co., 800 F.2d 1091,231 USPQ 375 (Fed. Cir. 1986). Clearly the examiner noted that Zhang while disclosing the peptide based urethane polymer may allow incorporation of proteins of interest such as cell attachment and/or growth factors but does not give any working examples, which is why the reference was combined with the other two other references in a 103(a) obviousness type of rejection. Clearly Zhang suggest incorporating proteins of interest in the peptide based urethane polymer but since the reference is silent on how to specifically attach such proteins one of ordinary skill in the art would seek such knowledge in the prior art. Such disclosure is provided by the secondary references Liptova and Woodhouse who both describe incorporation of bioactive agents into polyurethane polymers. Thus one of ordinary skill in the art would have a high expectation of success in conjugating bioactive substances such as peptides and heparin in the polyurethanes of Zhang since such knowledge was well known at the time of applicants claimed invention as taught in Liptova and Woodhouse and Zhang suggest incorporating proteins in the peptide based polyurethane.

Applicants respectfully traverse the Examiner's rejections and address each rejection below.

Section 102

Claims 1,3-11,15-16,18-20,22,25 and 69 are not anticipated under 35 U.S.C. 102(e) by Beckman et al. (US 7,264,823 B2)

Applicants respectfully assert that, under the appropriate standard as set forth in previous responses, Beckman et al. does not anticipate the presently claimed compositions and implants. Unlike the porous, foamed polymer compositions of the present invention, adhesives and other isocyanate-functional compositions of Beckman et al. are formed by first creating an isocyanate functional prepolymer by reacting an excess of a multifunctional isocyanate with one or more multifunctional precursor compound which include reactive hydrogen groups (-OH groups and/or -NH_2 groups). See, for example, Col. 9, lines 33-38. By necessity, the formation of the isocyanate functional prepolymers must be formed in the absence of water. As set forth previously, the presence of water in the reactions of Beckman et al. would cause reaction of all isocyanate functionality in the compounds of Beckman et al., and thereby render the compounds of Beckman et al. ineffective as adhesives. In the case of Beckman et al., in the example of the reaction of di-functional isocyanate with a di-amine functional precursor, represented by OCN-R_1-NCO and H_2N-R_2-NH_2, respectively, the resultant isocyanate functional prepolymer will have the formula OCN(R_1-R_2-R_1-R_2-R_1…)NCO, wherein the bonds between R_1 and R_2 are urea bonds. In the case of Beckman et al., in the example of the reaction of di-functional isocyanate with a di-hydroxyl functional precursor, represented by OCN-R_1-NCO and HO-R_2-OH, respectively, the resultant isocyanate functional prepolymer will have the formula OCN(R_1-R_2-R_1-R_2-R_1…)NCO, wherein the bonds between R_1 and R_2 are urethane bonds. As set forth in the specification and

examples of Beckman et al., isocyanate functional prepolymers/adhesives of relatively high molecular weight are formed, which react with tissue moisture and reactive hydrogen groups on tissue to cure.

Unlike the case of the precursor compounds of Beckman et al., in the presently claimed compositions and implants, multifunctional isocyanate compounds are reacted with at least one bioactive agent in a solution with a chain extender comprising water. In the presence of water, hydrolysis of the multifunctional isocyanate compounds occurs. In the case of the di-functional isocyanate OCN-R_1-NCO, reaction with water releases carbon dioxide gas (resulting in formation of a porous polymer foam in the final composition) and forms a di-amine having the formula H_2N-R_1-NH_2. This di-amine and the bioactive agent react both with the di-functional isocyanate.

In the example of the reaction of the di-functional isocyanate with a di-amine bioactive agent represented by H_2N-R_2-NH_2 or a di-hydroxyl bioactive agent represented by HO-R_2-OH, the resultant porous foamed polymer will not include only the repeat (R_1-R_2-R_1-R_2-R_1…) as in the prepolymers of Beckman et al. In that regard, the presently claimed porous foamed polymers and implants will include blocks of R_1 (the isocyanate residue) linked by urea bonds, represented, for example, by (R_1-R_1-R_1-R_2-R_1-R_1-R_2-R_1), which is different chemical structure than the compositions of Beckman et al., exhibiting different properties and *in situ* behavior. The bonds between R_1-R_2-R_1 portions of the resultant polymer will be urea bonds or urethane bonds depending upon the functionality of the bioactive agent(s).

Moreover, the presence of water during the first reaction of the multifunctional isocyanate and the bioactive agent as in the presently claimed compositions and implants affects the manner in which the bioactive agent is incorporated into the resultant polymer as compared to the case of Beckman et al, wherein all reactive hydrogen precursors are first reacted with an excess of multifunctional isocyanate in the absence of water.

For example, when polymerization reaction occurs in the presence of unmodified bioactive agent in an aqueous environment (as opposed to in the environment of Beckman et al, wherein a prepolymer is formed in the absence of water), the nature of the incorporated bioactive agent can vary. For example, unlike the case of Beckman et al, it is possible to both covalently bond and also entrain unreacted bioactive agent into the forming polymer in the case that a statistical fraction

of the bioactive agent molecules do not react with the polymer forming units. Such unmodified bioactive agent is physically present in the polymer, but is not covalently anchored. Such entrained bioactive agent can, for example, diffuse away from the polymer in the early stages of placement *in situ*.

Moreover, unlike the case of Beckman et al., a statistical fraction of the bioactive agent may participate in some reaction with the polymer forming units, but the degree of modification, or the degree of polymerization of units attached to the bioactive agent may be relatively low. Such minimally modified bioactive agent can, for example, be released/delivered more quickly from the polymer when placed *in situ* than the case of a bioactive agent linked into polymer having a higher degree of modification or degree of polymerization.

A statistical fraction of the bioactive agent which participates to a high degree in reactions with the polymer forming units will be well anchored (covalently) into the polymer network and will be expected to have the longest residence in the delivered polymer.

This statistical range of possibilities is not possible in the adhesives of Beckman et al. because all reactive hydrogen precursors are first reacted with an excess of multifunctional isocyanate in the absence of water to react all or substantially all of the reactive hydrogen groups thereof in forming an isocyanate functional prepolymer. The kinetics of release of the bioactive agents of the presently claimed compositions and implants will be different than the kinetics of release of the reactive hydrogen functional precursors of Beckman et al.

Applicants thus respectfully assert that, contrary to the Examiner's assertions, the presence of water during the reaction of the bioactive agents with multifunctional isocyanates results in polymers of different composition and physiological characteristics than the adhesives of Beckman et al.

Claims 1,3-4,7-8,12,19,22,27-30,33 and 69 under are not anticipated under35 U.S.C. 102(e) by Woodhouse et al. (US 6,221,997 B1)

Applicants respectfully assert that, under the appropriate standard as set forth in previous response, Woodhouse et al. does not anticipate the presently claimed compositions and implants. Although Woodhouse et al. discloses the incorporation of certain amines or oligopeptides into the

polymers thereof as recognized by the Examiner, the amines or oligopeptides are first reacted with another component via an esterification reaction to be formed into a chain extender including the amine or oligopeptide residue. See, for example, formulas (A) through (D) of in cols. 2 and 3. Such chain extenders are subsequently reacted with an isocyanate functional prepolymer or a di-isocyanate in the absence of water. See, for example, col. 2, line 24 to col. 3, line 30 and the examples. The esterification reactions of the amines or oligopeptides and subsequent reactions with an isocyanate in the absence of water result in a different composition than in the presently claimed compositions and implants wherein a bioactive agent is reacted directly with a multi-functional isocyanate in the presence of a chain extender including water. As discussed above, multifunctional isocyanate compounds react directly with the bioactive agent and with the water in forming a porous foamed composition. The presently claimed foamed polymer compositions and implants are very different from the polymers of Woodhouse et al. in their chemical composition and in their physiochemical properties. For example, as discussed above, unlike Woodhouse et al., the presently claimed compositions and implants include isocyanate residues connected by urea bonds (resulting from reaction of the multifunctional isocyanate with di-amines formed by reaction of the multifunctional isocyanate with water). As also discussed above, the incorporation of bioactive agents in the claimed compositions and implants as well as the kinetics of release of bioactive agents from the claimed compositions and implants is different from that of Woodhouse et al. Moreover, unlike the case of Woodhouse et al., the release of carbon dioxide as a result of the reaction of multifunctional isocyanate with water, results in a porous foamed morphology.

Section 103

Claims 1,3-11,15-16,18-26 and 69 under are not unpatentable under 35 U.S.C. 103(a) over Zhang et at. (Biomaterials 21 (2000) 1247-1258) in view of Liptova et al. (Macromol. Symp. 152, 139-150 (2000)) or in view of Woodhouse et at. (US 6,221,997 B1)

For the reasons discussed in connection with Beckman et al., Zhang et al. does not disclose or suggest the presently claimed compositions and implants in which a bioactive agent is reacted with a multifunctional isocyanate in solution with a chain extender comprising water. Similar to Beckman et al. and unlike the presently claimed invention, Zhang et al. discloses the reaction of a polyol (glycerol) with an excess of di-isocyanate in the absence of water to from a crosslinked

prepolymer. In the prepolymer of Zhang et al., glycerol residues are interconnected or crosslinked via urethane linkages with isocyanate residues in alternating manner.

For the reasons set forth above and in previously filed responses, one cannot combine the disclosure of Zhang et al. with the disclosure of Lipatova et al., Woodhouse et al. and/or any combination thereof to arrive at the present invention. Lipatova et al. and Woodhouse et al. disclose the incorporation of various entities into a polyurethane polymer. However, neither Lipatova et al. nor Woodhouse et al. disclose or suggest a reaction of at least one multifunctional isocyanate compound with at least one bioactive agent as set forth in the present claims in a solution with a chain extender comprising water as set forth in the present claims so that the multifunctional isocyanate compound reacts with the at least one bioactive agent and with the water to form a porous foam. Once again, the polymers of Lipatova et al. and Woodhouse et al. are formed in the absence of water.

Contrary to the Examiner's assertions, the polymer compositions of Zhang et al., Lipatova et al. and Woodhouse et al. are different in chemical structure and physiological characteristics than the presently claimed compositions and implants.

In view of the above amendments and remarks, Applicants respectfully requests that the Examiner, indicate the allowability of the Claims, and arrange for an official Notice of Allowance to be issued in due course.

Respectfully submitted,
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